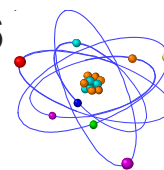


# LABORATORY SAFETY FACT SHEET #26



## Synthesizing, Purifying, and Handling Organic Azides

Organic azides are potentially-explosive substances that can and will decompose with the slightest input of energy from external sources (heat, light, pressure). Additionally, small molecules containing the azido functionality tend to decompose violently which may result in injury if proper safety precautions are not utilized.

Organic azides have received renewed interest for their sheer diversity of potential organic transformations but also in no small part to the recent introduction of the concept of 'Click Chemistry.'<sup>1</sup> This renewed interest must be paralleled with a reiteration of the safety precautions one must undertake. In addition to summarizing the multitude of these synthetic transformations in which azide can participate, recent reviews have also outlined safety precautions one should take when utilizing these energy-rich molecules. These manuscripts should be mandatory reading for anyone working with, or around azides.<sup>2</sup>

Obtained by simple nucleophilic displacement of a halogen or by copper (I)-catalyzed aryl coupling, organic azides can be prepared, purified, and handled safely provided one takes the following precautions:

### **NaN<sub>3</sub>:**

- Azide ion has a similar toxicity as that of cyanide ion ( $LD_{50} = 27 \text{ mg/kg}$  for rats). Be sure to use appropriate gloves when weighing azido salts.
- Sodium azide reacts violently with several common laboratory organics such as: CS<sub>2</sub>, bromine, Bronstead acids, and heavy metals. When attempting a new reaction, be relentless in your background research to determine the reactivity of sodium azide to ALL reaction components.
- NEVER use chlorinated solvents as reaction media! Utilizing dichloromethane or chloroform will result in the formation of explosively-unstable di- and tri- azidomethane, respectively (refer to section on C/N ratios below).
- Heavy metals (e.g., Cu, Pb, Ba) form shock and pressure sensitive compounds with azide anions. This may affect us in that an 'azide residue' may form of metal parts.

### **Organic Azides:**

- All organic azides decompose with introduction of external energy. Any azide synthesized should be stored below room temperature (-18°C) and in the dark.
- When designing your target azide, keep in mind the following equation.<sup>1</sup> Notice that this equation takes into account all nitrogen atoms in your azide, not just those in the azido group. *N* signifies the number of atoms.

$$\frac{N_C + N_O}{N_N} \geq 3 \quad (\text{eq. 1})$$

- In practice, organic azides that contradict the above equation can be made, and in some cases, be stored safely. Consider the following points as strict guidelines in the preparation and storage of organic azides. As with all synthetic procedures a small scale (ca. 0.5-1.0 gram) should be run first to determine the nature of the product:
  - *n*-nonyl azide (C/N=3) will be the smallest azide isolated and stored in its pure form. This azide, when stored properly, can be done so in multigram quantities (up to 20 grams). In practice, the octyl derivative is equally safe (C/N=2.7).
  - Azides smaller than C/N=3 (but greater than C/N=1) can be synthesized and isolated, but by no means should these molecules be stored in its highest purity. Rather, if storage is necessary store these azides as solutions below room temperature (concentrated to no more than 1M, less than 5 grams material).
  - Under no circumstances should azides with C/N < 1 be isolated. However, these molecules may only even be considered for synthesis if the azide is a transient intermediate species, AND the limiting reagent in the reaction mixture, AND with maximum quantities of 1 grams. For instance, methyl azide can be synthesized in situ and immediately reacted with an excess of a terminal acetylene.<sup>1</sup>
- Never use distillation or sublimation as purification techniques! Purification should be limited to extraction and precipitation. Column chromatography may contribute to decomposition so only purify azides that satisfy equation 1.
- Organic azide waste should be placed in a separate, explicitly-labeled container designated solely for azide waste. Extra caution must be taken to make certain that azide waste not come in contact with acid. Acids will protonate the azide ion and form the highly-toxic hydrogen azide (toxicity similar to that of hydrogen cyanide).

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<sup>1</sup>. Kolb, H.C.; Finn, M.G.; Sharpless, K.B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.

<sup>2</sup>. Brase, S.; Gil, C.; Knepper, K.; Zimmerman, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240. And all references therein.

<sup>3</sup>. Smith, P.A.S. *Open-Chain Nitrogen Compounds*, vol. 2, Benjamin, New York, 1966, 211-265.

<sup>4</sup>. Feldman, A.K.; Colasson, B.; Fokin, V.V. *Org. Lett.* **2004**, *6*, 3897. Thibault *et al.* manuscript in preparation